REMARKS

Claims 1, 7, 10, and 17 have been amended. Claims 1 and 17 have been amended to include sequence identifiers. Claims 7 and 10 have been amended to correct typographical errors. No new matter has been added. Applicant respectfully requests reconsideration and allowance of claims 1, 3-14, 16 and 17 in view of the above amendments and following remarks.

Enclosed herewith are replacement copies of references AG and AH, listed on the Form 1449 submitted with the Information Disclosure Statement of September 21, 1999. Applicant respectfully requests that an initialed copy of the Form 1449 be returned to Applicant, indicating that references AG and AH have been considered by the Examiner. Applicant notes that the Form 1449 contains a typographical error for reference AG: "J. Can. Invest." should be "J. Clin. Invest."

Sequence Listing

The Examiner asserts that the application is not in compliance with the sequence listing requirements as the claims recite specific amino acid residues of the Factor VII or Factor VIIa polypeptide by position number and a sequence identifier is not identified. According to the Examiner, "[s]uch a sequence identifier must be in the claims for the numbers to have any significance and [so that] the claims [can] properly be searched."

Applicant has amended independent claims 1 and 17 to include sequence identifiers. As indicated in the response of June 18, 2001, the amino acid positions of the polypeptides are numbered according to factor IX throughout the specification. As factor VII has one less amino acid (position 4), the numbering of the amino acid positions must be adjusted accordingly. See, specification at page 9, lines 14-19. Thus, when a claim recites a particular position, such as amino acid 11 of factor VII or VIIa, the position is actually position 10 of factor VII or VIIa in the sequence listing. Applicant submits the application is in compliance with the requirements of 37 C.F.R. §1.82 – 1.825.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 1, 2-14, 16 and 17 under 35 U.S.C. §112, first paragraph, for lack of written description. The Examiner asserted that Applicant's

statement that "it would be apparent to a person of ordinary skill in the art that polypeptide fragments could be produced" was not "indicative of the applicants' possession of the claimed subject matter at the time of filing, especially in view of the lack of any reference(s) showing what is/was apparent to a person of skill in the art at the time of this application." The Examiner further asserted that since "no fragment(s) were produced by the applicant", arguments drawn to "a fragment of the polypeptide used in determining membrane affinity (pages 24-25 of the specification) of factor VII polypeptide carries little or no weight regarding the possession of the fragments of the polypeptide." Applicant respectfully traverses this rejection.

Claims 1, 3-14 and 16 are drawn to a factor VII or factor VIIa polypeptide having a modified GLA domain containing at least one substitution at amino acid residue 11 or 29 and having enhanced membrane binding affinity relative to a corresponding native factor VII or factor VIIa polypeptide. Claim 17 is drawn to a factor VII or factor VIIa polypeptide having a modified GLA domain containing an aspartic acid residue at amino acid 33 and having enhanced membrane binding affinity relative to a corresponding native factor VII or factor VIIa polypeptide.

Applicant does not need to submit a reference showing "what is/was apparent to a person of skill in the art at the time of filing of this application." As indicated in §2163 of the MPEP, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims in not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient")."

Applicant was in possession of the claimed factor VII and VIIa polypeptides. As previously indicated, the nucleotide and amino acid sequences of the entire bovine and human factor VII polypeptides were known at the time of filing. The specification provides the GenBank Accession number as well as a reference for the wild type factor VII cDNA. See, the specification at page 23, lines 4-6. Furthermore, the wild-type amino acid sequences for the

GLA domains of human and bovine factor VII (SEQ ID NOS: 3 and 4, respectively) are provided at page 12, lines 15-16 of the specification.

The specification also describes how to make polypeptides of the invention, including full-length factor VII polypeptides and fragments of full-length factor VII polypeptides. For example, Example 1 describes the production of full-length factor VII with enhanced membrane binding affinity using a polymerase chain reaction (PCR) strategy. PCR primers are denoted by nucleotide location. See, for example, page 23, lines 13-16. Nucleic acid fragments were generated with this strategy, and ligated to produce a nucleic acid encoding a full-length polypeptide. It would be apparent to a person of ordinary skill in the art that fragments of full-length factor VII polypeptides could be produced from these or other nucleic acid fragments in the same manner. Detailed methods also are provided for the purification of factor VII. See, for example, page 24, lines 3-9 and Example 2, page 30, line 21 through page 31, line 26.

Furthermore, the specification describes techniques for determining membrane affinity of factor VII polypeptides. In general, vesicles of phosphatidylserine and phospatidylcholine were prepared, and protein was added at different weight ratios. Protein-membrane binding then was assayed by a light scattering technique. See, specification, page 24, line 20 through page 25, line 20. Thus, Applicant was in possession of factor VII or VIIa polypeptides comprising the GLA domain of factor VII as well as the full-length polypeptide. In view of the above remarks, the Examiner is requested to withdraw the rejection of claims 1-14, 16, and 17 under 35 U.S.C. §112, first paragraph, for lack of written description.

The Examiner rejected claims 1, 3-14, 16, and 17 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner asserted that the claims call for amino acid substitutions at exact residues 11, 29 and/or 33 of the GLA domain, while the GLA domain contains the N-terminal region of the polypeptide, "typically from amino acid 1 to amino acid 45." The Examiner further asserted that "[t]ypically is not indicative of a specific amino acid being substituted at a specific site in a known sequence of a polypeptide – as claimed. Therefore, enablement is lacking for the claims." Applicant respectfully disagrees with the Examiner.

Claims 1, 3-14, 16, and 17 recite polypeptides that comprise substitutions at particular residues. The specification enables one of ordinary skill in the art to make and use such polypeptides. As previously indicated, the nucleotide and amino acid sequences of the entire

bovine and human factor VII polypeptides were known at the time of filing. The specification provides the GenBank Accession number as well as a reference for the wild type factor VII cDNA. See, the specification at page 23, lines 4-6. Furthermore, the wild-type amino acid sequences for the GLA domains of human and bovine factor VII (SEQ ID NOS: 3 and 4, respectively) are provided at Table 2, page 12, lines 15-16 of the specification.

The specification also provides detailed guidance to the numbering of the amino acid positions within factor VII. As indicated in the specification at page 9, lines 14-19, the polypeptides are numbered according to factor IX throughout the specification. As factor VII has one less amino acid (position 4), the numbering of the amino acid positions must be adjusted accordingly, as indicated at page 9, lines 14-19 of the specification. Thus, when an amino acid residue is provided, such as amino acid 11 of factor VII or VIIa, the position is actually position 10 of factor VII or VIIa in the sequence listing. Applicant submits that one of ordinary skill in the art would understand the location of positions 11, 29, and 33 within factor VII or VIIa.

It also is apparent from the specification that the GLA domain is located on the amino terminal portion of factor VII. See, for example, page 9, lines 10-11, of the specification, which indicates that the GLA domain contains 9-13 γ-carboxyglutamic acid residues in the N-terminal region of the polypeptide, typically from amino acid 1 to amino acid 45. See also Table 2, page 12, lines 15-16, which provides the GLA domain of human and bovine factor VII. Applicant also submits that one of ordinary skill in the art would understand that positions 11, 29, and 33 fall within the GLA domain of factor VII or VIIa.

Thus, the specification provides adequate information to allow one of ordinary skill in the art to produce the claimed polypeptides. In view of the above remarks, the Examiner is requested to withdrawn the rejection of claims 1, 3-14, 16, and 17 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 2-14 and 16 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserted that the "claims are indefinite and confusing as to which amino acid is being replaced . . . and the sequence of the amino acids claimed . . . which

shows the exact position of the substitution in the sequence." The Examiner also asserted that sequence identifiers are required for a proper search.

Independent claim 1 has been amended to include sequence identifiers. Applicant submits that claims 1, 2-14, and 16 are sufficiently definite. As indicated in the specification on page 9, lines 15-19, some vitamin K dependent polypeptides, including protein C and with factor VII, "have one less amino acid (position 4) and must be adjusted accordingly. See, specification at page 9, lines 14-19. For example, actual position 10 of bovine protein C is a proline, but is numbered herein as amino acid 11 for ease of comparison throughout." Thus, "residue 11" recited in the claims corresponds to the 10^{th} amino acid residue from the N-terminal end of factor VII or factor VIIa; "residue 29" recited in the claims corresponds to the 28^{th} amino acid residue from the N-terminal end of factor VII or factor VIIa; and "residue 33" recited in the claims corresponds to the 32^{nd} amino acid residue from the N-terminal end of factor VII or factor VIIa. One of ordinary skill in the art can readily identify the precise amino acid positions to be substituted based on the teachings of the specification and the identifiers provided in the claims.

The specification provides a number of examples of amino acid residues that can be substituted at positions 11, 29, and 33. The specification indicates conservative or non-conservative substitutions can be made. In addition, the specification indicates that a glutamic acid, a glutamine, an asparagine, or an aspartic acid residue can be substituted at amino acid 11, or a phenylalanine or glutamic acid residue can be substituted at amino acid 29. The specification indicates that an aspartic acid or glutamic acid can be substituted at amino acid 33. The specification also provides guidance on how to make such modified factor VII polypeptides and measure membrane affinity of modified factor VII polypeptides. Thus, Applicant submits that claims 1, 3-14, and 16 are sufficiently definite under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicant submits that claims 1, 3-14, 16, and 17 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if it is felt that such would advance prosecution of the application.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant : Gary L. Nelsestuen
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Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 1/7/02

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Version with markings to show changes made

In the claims:

Claims 1, 7, 10, and 17 have been amended as follows:

1. (Twice amended) A Factor VII or Factor VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at residue 11 or 29 (residue 10 or 28 of SEQ ID NO:3 or SEQ ID NO:4. respectively).

. 7. (Twice amended) The polypeptide of claim 1, wherein said modified GLA domain further comprises an amino acid substitution at residue 33.

10. (Amended) The polypeptide of claim 5, wherein said modified GLA domain further comprises a substitution of a glutamic acid or an aspartic acid at residue 33.

17. (Twice amended) A Factor VII or Factor VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor VIIa polypeptide, said modified GLA domain comprising an aspartic acid residue at amino acid 33 (residue 32 of SEQ ID NO:3 or SEQ ID NO:4).